Efficacy and Safety of Ticagrelor Monotherapy in Patients Undergoing Percutaneous Coronary Intervention: A Meta-Analysis

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Dual antiplatelet therapy (DAPT) and subsequent $P2Y_{12}$ inhibitor monotherapy, particularly ticagrelor, is an emerging treatment strategy in patients undergoing percutaneous coronary intervention (PCI). This meta-analysis was designed to investigate whether short-term DAPT followed by ticagrelor monotherapy is associated with a favorable outcome as compared with standard DAPT (1–3 months of DAPT was termed "short-term" DAPT, 6–12 months DAPT was termed "standard" DAPT). The primary outcome was the composite of major adverse cardiovascular events (MACE) comprising myocardial infarction, stroke, and cardiovascular death. Secondary outcomes included all-cause mortality and net adverse clinical events (NACE; myocardial infarction, stroke, all-cause death, stent thrombosis, and major bleeding). The primary safety outcome was major bleeding. Three studies comprising 26,143 patients were included. The risk of MACE was similar between the two treatment groups (risk ratio (RR) 0.86, 95% confidence interval (CI), 0.72–1.02, $P = 0.08$, $I^2 = 22\%$). Short-term DAPT followed by ticagrelor monotherapy resulted in a 20% relative risk reduction of all-cause mortality (RR 0.80, 95% CI, 0.65–0.98, $P = 0.03$, $I^2 = 0\%$) and an 18% relative risk reduction of NACE (RR 0.82, 95% CI, 0.71–0.94, $P = 0.005$, $I^2 = 33\%$) as compared with standard DAPT. Short-term DAPT followed by ticagrelor monotherapy significantly decreased the risk of major bleeding (RR 0.67, 95% CI, 0.49–0.92, $P = 0.01$, $I^2 = 65\%$). In patients with acute coronary syndrome, short-term DAPT followed by ticagrelor monotherapy resulted in an unchanged ischemic risk but a significantly lower bleeding risk compared with standard DAPT. Short-term DAPT followed by ticagrelor monotherapy compared with standard DAPT resulted in a favorable safety and efficacy profile. Direct comparisons of aspirin vs. ticagrelor monotherapy following PCI are needed.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Dual antiplatelet therapy (DAPT) is effective in preventing thromboembolic complications following percutaneous coronary intervention (PCI) but is associated with an increased risk of bleeding. $P2Y_{12}$ inhibitor monotherapy, as opposed to aspirin monotherapy, has emerged as an up-and-coming treatment regimen following DAPT.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study sought to evaluate the efficacy and safety of ticagrelor monotherapy following PCI.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Short-term DAPT (1–3 months) followed by ticagrelor monotherapy was associated with less all-cause mortality, net adverse clinical events, and major bleeding but an unchanged risk of ischemic events compared with standard DAPT (12 months).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Short-term DAPT followed by ticagrelor monotherapy is safe and effective and may present an attractive treatment regimen in patients with a high bleeding risk.

Dual antiplatelet therapy (DAPT), defined as a combination of aspirin plus a $P2Y_{12}$ inhibitor, has become the cornerstone treatment in patients with acute coronary syndrome (ACS) or undergoing planned percutaneous coronary intervention (PCI).[1,2] For patients with stable coronary artery disease undergoing PCI and no high bleeding risk, current guidelines, from both the European Society

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of Cardiology (ESC) and the American College of Cardiology (ACC)/American Heart Association (AHA), recommend DAPT with clopidogrel for the duration of 6 months.[1,2] For patients with ACS that are being treated with PCI, both guidelines suggest DAPT for a period of 12 months, with a class IIb recommendation to continue DAPT for an extended period over 1 year.

However, due to the increased risk of bleeding complications accompanying DAPT and associated compliance/adherence problems, shortening of DAPT or switching to single antiplatelet therapy have become options in patients undergoing PCI.[3] In contrast to primary prevention,[4] aspirin's efficacy in secondary prevention of cardiovascular disease is well-established,[5] but its status as cornerstone treatment in antithrombotic therapy is being challenged due to the (i) increased bleeding events (especially with concomitant $P2Y_{12}$ inhibitor use or anticoagulation and in the elderly population),[6] (ii) reduction of cardiovascular events by other cardiovascular drug classes, and (iii) and the introduction of other potent antiplatelet agents.[7] Furthermore, the development of newer-technology drug-eluting stents with ultra-thin struts and bioresorbable polymers warrants stratified approaches toward duration of DAPT.[8–12]

These changes have prompted studies investigating $P2Y_{12}$ inhibitor monotherapy with ticagrelor. This meta-analysis summarizes studies on $P2Y_{12}$ inhibitor monotherapy with ticagrelor after PCI and discusses their clinical implications.

METHODS

Data sources

Our trial was registered with PROSPERO under the ID CRD42020211516. We conducted a systematic search in the PubMed, Cochrane, Embase, and Web of Science from database inception through the final search date of June 30, 2020. We used the subsequent predefined search terms: ticagrelor monotherapy AND dual antiplatelet therapy AND duration AND bleeding. No language, publication date, or publication status restrictions were applied. References of retrieved articles and prior meta-analyses were checked for additional studies.

Trial eligibility and data extraction

This study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Table S1**) and performed according to established methods, as described previously.[13,14] Only full-text articles were included. Trials that (i) compared any different DAPT durations after PCI and used ticagrelor monotherapy, (ii) were randomized controlled trials, and (iii) reported on at least one of the outcomes of interest (major adverse cardiovascular events (MACE), myocardial infarction (MI), stroke, stent thrombosis (ST), all-cause death, cardiovascular death, and major bleeding) were included. Eligible reports were assessed for methodological quality using the Cochrane Risk of Bias Tool (**Table S2**). Studies were excluded if one could determine, from the title, or abstract, or both, that the study was not suitable for inclusion. Full text of the study was obtained and evaluated if an article could not be excluded with certainty. Two reviewers (authors G.G. and J.M.S.M.) independently and in duplicate applied the selection criteria. Any discrepancy was resolved by author consensus.

Outcomes and subgroup analysis

The primary efficacy outcome was the composite of MACE (the composite of MI, stroke, and cardiovascular death). The secondary efficacy outcomes included all-cause death, cardiovascular death, MI, ST, and stroke. We also calculated the composite of net adverse clinical events (NACE; composite of MI, stroke, all-cause death, ST, and major bleeding). Major bleeding was defined as the primary safety outcome. Two different bleeding definitions, Thrombolysis in Myocardial Infarction (TIMI)[15] and Bleeding Academic Research Consortium (BARC),[16] were used in the trials included in this meta-analysis.

All outcomes were analyzed by an intention-to-treat analysis. We performed subgroup analyses for the primary efficacy outcome and the primary safety outcome, including only patients presenting with ACS and patients undergoing complex or noncomplex PCI. The definitions of complex PCI differed in the GLOBAL LEADERS and the TWILIGHT trial. Details about the differences between the definitions of complex PCI are shown in **Table S3**.

Due to the heterogenous definitions of MACE and NACE used, we performed sensitivity analyses using the MACE/NACE definitions from each individual study.

Data synthesis and statistical analysis

DAPT durations were categorized into short-term DAPT (1–3 months) and standard DAPT (6–12 months). Variables were reported as number or percentages, as appropriate. Risk ratios (RRs) were computed from individual studies and pooled according to the inverse variance random effect method with 95% confidence intervals (CIs) using Review Manager (version 5.4; The Cochrane Collaboration, 2020). Unadjusted P values were reported throughout, with hypothesis testing set at the 2-tailed significance level of 0.05. We assessed studies for clinical and statistical heterogeneity. To assess statistical heterogeneity, we calculated the I^2 index and a P value. Percentages < 25% ($I^2 = 25$), 25–50% ($I^2 = 50$), and 50–75% ($I^2 = 75$) correlate to low, medium, and high heterogeneities, respectively.[17] Due to the high clinical heterogeneity, we used the random-effect model.

RESULTS

Our search yielded 74 references. The flow diagram depicting our search algorithm is shown in **Figure S1**. Three studies, including a total of 26,143 patients, met our inclusion criteria.[18–20] The TWILIGHT[19] and the TICO trials[18] both had a follow-up of 12 months. The GLOBAL LEADERS trial[20] provided a 2-year follow-up, yet for consistency of data, we chose to include data from the 1-year follow-up. Further, the GLOBAL LEADERS trial[20] did not report on the outcome of cardiovascular mortality, so all-cause mortality was used for the composite end point MACE.

Specific data for the ACS subgroup of the GLOBAL LEADERS was taken from a *post hoc* analysis.[21] In the same manner, data for the complex/noncomplex PCI subgroups were taken from *post hoc* analyses from the GLOBAL LEADERS[22] and the TWILIGHT trials.[23] Data from the GLOBAL LEADERS trial for the sensitivity analysis of NACE was taken from another *post hoc* analysis.[24]

All studies[18–20] exclusively included patients who underwent PCI with placement of a drug-eluting stent. The TWILIGHT trial included patients with high ischemic or bleeding risk but excluded patients presenting with ST-elevation MI.[19] The TICO trial only included patients presenting with ACS but excluded patients with an increased risk of bleeding.[18] Detailed information on the studies included can be found in **Table 1** and **Table S4**.

Primary efficacy outcome: Major adverse cardiovascular events

Short-term DAPT followed by ticagrelor monotherapy was associated with a trend toward a decreased risk of MACE (RR

Table 1 Table depicting characteristics of included studies

Study	Design	Follow-up	$P2Y_{12}$ inhibitor	Duration	*N*	Study population	DES type
Vranckx *et al.* GLOBAL LEADERS	Open-label, randomized superiority trial	12 months/730 days (24 months)	Ticagrelor	1 month vs. 12 months	15,968 7,980 vs. 7,988	ACS and stable CAD	Biolimus-eluting stent
Mehran *et al.* TWILIGHT	Randomized, placebo-controlled, double-blind, multicenter trial	12 months	Ticagrelor	3 months vs. 12 months	7,119 3,555 vs. 3,564	ACS and stable CAD	DES
Kim *et al.* TICO	Investigator-initiated, multicenter, randomized, unblinded trial	12 months	Ticagrelor	3 months vs. 12 months	3,056 1,527 vs. 1,529	ACS	Ultrathin bioresorbable polymer sirolimus-eluting stents

ACS, acute coronary syndrome; CAD, coronary artery disease; DES, drug-eluting stent.

0.86, 95% CI, 0.72–1.02, $P = 0.08$, $I^2 = 22\%$; **Figure 1a**) compared with standard DAPT. The absolute risk reduction, number needed to treat, and number of events reduced per 1,000 patients treated of the major outcomes of this study are shown in **Table 2**.

Secondary efficacy outcomes

Short-term DAPT followed by ticagrelor monotherapy resulted in a significant 18% relative risk reduction of the composite of NACE as compared with standard DAPT (RR 0.82, 95% CI, 0.71–0.94, $P = 0.005$, $I^2 = 33\%$; **Figure 1b**), resulting in a favorable net clinical benefit.

Short-term DAPT followed by ticagrelor monotherapy was associated with a significant 20% relative risk reduction of all-cause death (RR 0.80, 95% CI, 0.65–0.98, $P = 0.03$, $I^2 = 0\%$; **Figure 1c**), as compared with standard DAPT.

Two trials, the TWILIGHT[19] and the TICO trials,[18] reported on the outcome of cardiovascular death. Short-term DAPT was associated with a similar risk of cardiovascular death as compared with standard DAPT (RR 0.68, 95% CI, 0.44–1.05, $P = 0.08$, $I^2 = 0\%$; **Figure S2a**).

There were no statistically significant differences between short-term DAPT followed by ticagrelor monotherapy and standard DAPT regarding the relative risk of MI (RR 1.06, 95% CI, 0.88–1.27, $P = 0.57$, $I^2 = 11\%$; **Figure S2b**), ST (RR 1.14, 95% CI, 0.80–1.62, $P = 0.48$, $I^2 = 4\%$; **Figure S2c**), stroke (RR 1.13, 95% CI, 0.73–1.76, $P = 0.58$, $I^2 = 27\%$; **Figure S2d**) or target vessel revascularization (RR 0.87, 95% CI, 0.75–1.02, $P = 0.10$, $I^2 = 0\%$; **Figure S2e**).

Primary safety outcome: Major bleeding

One study[18] reported on the major bleeding outcome according to the TIMI bleeding classification and all three studies[18–20] according to the BARC bleeding classification.

Short-term DAPT followed by ticagrelor monotherapy significantly decreased the risk of major bleeding (according to the BARC bleeding classification) compared with standard DAPT (RR 0.67, 95% CI, 0.49–0.92, $P = 0.01$, $I^2 = 65\%$; **Figure 2**).

Subgroup analysis: Acute coronary syndrome

All three studies provided data on the ACS subgroup.[18,19,21]

In patients presenting with ACS, standard DAPT was associated with an unchanged risk of MACE compared with short-term DAPT followed by ticagrelor monotherapy (RR 0.91, 95% CI, 0.74–1.12, $P = 0.38$, $I^2 = 15\%$; **Figure 3a**).

Patients with ACS receiving short-term DAPT followed by ticagrelor monotherapy had significantly lower risk of major bleeding compared with patients with ACS receiving standard DAPT (RR 0.50, 95% CI, 0.40–0.61, $P < 0.00001$, $I^2 = 0\%$; **Figure 3b**).

Subgroup analysis: Complex/noncomplex PCI

Post hoc analyses from two trials, GLOBAL LEADERS[22] and TWILIGHT,[23] provided data on patients undergoing complex or noncomplex PCI.

In patients undergoing complex PCI, short-term DAPT followed by ticagrelor monotherapy was associated with a significantly

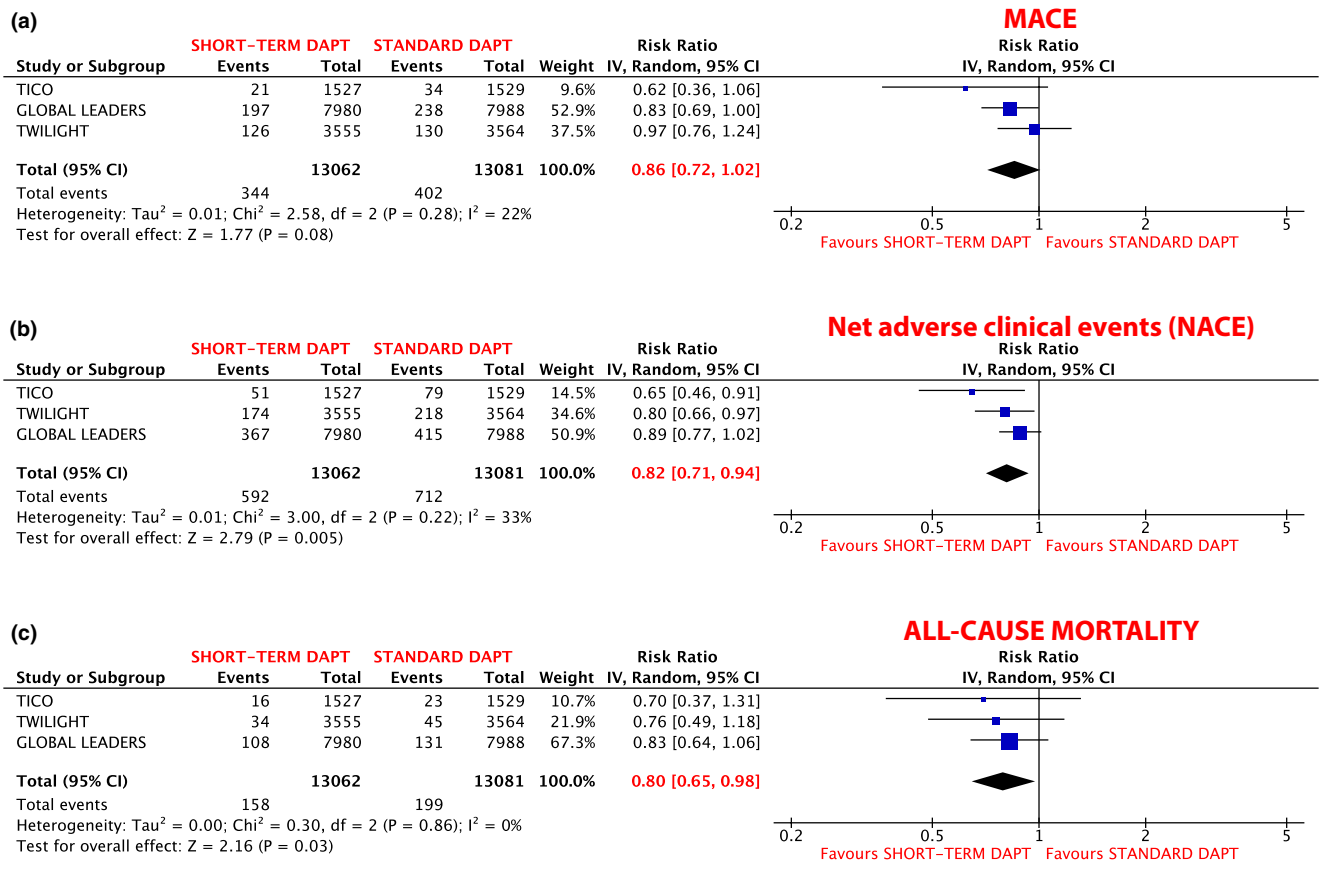

Figure 1 Forest plot showing the risk ratio of (**a**) major adverse cardiovascular events (MACE), (**b**) net adverse clinical events (NACE) and (**c**) all-cause mortality according to the two treatment regimens: short-term dual antiplatelet therapy (DAPT) followed by ticagrelor monotherapy vs. standard DAPT. CI, confidence interval.

Table 2 The RRR, ARR, the NNT, the number of events reduced per 1,000 patients treated, and the *P* value of the major outcomes of this study

	RRR, %	ARR, %	NNT	No. of events reduced per 1,000 treated patients	*P* value
MACE	14	0.4	250	4	0.08
NACE	18	0.9	111	9	**0.005**
All-cause mortality	20	0.3	333	3	**0.03**
Major bleeding	33	0.6	167	6	**0.01**

ARR, absolute risk reduction; MACE, major adverse cardiovascular event; NACE, net adverse clinical event; NNT, number needed to treat; RRR, relative risk reduction.
Bold indicates the values $P < 0.05$ are statistically significant.

lower risk of MACE compared with standard DAPT (RR 0.72, 95% CI, 0.56–0.93, $P = 0.01$, $I^2 = 0\%$; **Figure 3c**). There was no difference between treatment groups in patients undergoing noncomplex PCI (RR 0.98, 95% CI, 0.78–1.23, $P = 0.84$, $I^2 = 33\%$; **Figure 3c**).

In patients undergoing complex or noncomplex PCI, there was no significant difference between treatment groups, however, both subgroups showed a trend toward a reduction of major bleeding in the short-term DAPT followed by ticagrelor monotherapy group (RR 0.62, 95% CI, 0.30–1.30, $P = 0.21$, $I^2 = 72\%$; **Figure 3d** and RR 0.74, 95% CI, 0.48–1.14, $P = 0.17$, $I^2 = 54\%$, respectively; **Figure 3d**).

Sensitivity analysis: MACE (according to the individual studies' definition)

When the individual studies' definition of MACE was used, short-term DAPT followed by ticagrelor monotherapy significantly decreased the risk of MACE (RR 0.86, 95% CI, 0.74–0.99, $P = 0.04$, $I^2 = 10\%$; **Figure S3a**) compared with standard DAPT.

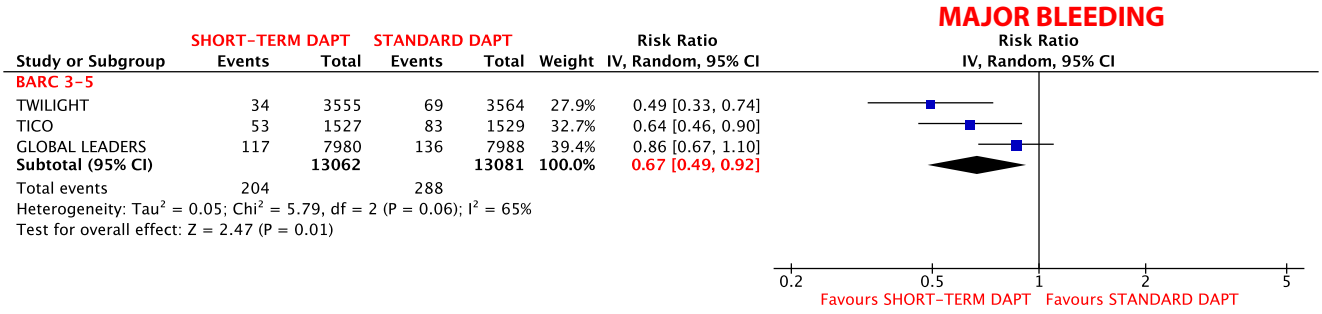

Figure 2 Forest plot showing the risk ratio of major bleeding (Bleeding Academic Research Consortium (BARC) 3–5) according to the bleeding academic research consortium in the two treatment regimens: short-term dual antiplatelet therapy (DAPT) followed by ticagrelor monotherapy vs. standard DAPT.

Sensitivity analysis: NACE (according to the individual studies' definition)

The GLOBAL LEADERS trial[24] and the TICO trial[18] reported on the incidence of NACE. When the individual studies' definition of NACE was used, there was no statistically significant difference between short-term DAPT followed by ticagrelor monotherapy and standard DAPT regarding the relative risk of NACE (RR 0.81, 95% CI, 0.59–1.11, P = 0.19, I^2 = 73%; **Figure S3b**).

DISCUSSION

This systematic review and meta-analysis comprise three trials (> 26,000 patients) investigating the novel concept of ticagrelor monotherapy in patients undergoing PCI following a short-term treatment with DAPT. All included studies compared short-term DAPT (1–3 months) followed by $P2Y_{12}$ inhibitor monotherapy with ticagrelor to standard DAPT (12 months).

Our meta-analysis shows that short-term DAPT followed by ticagrelor monotherapy is safe and effective. In particular, we demonstrate that, compared with standard DAPT, short-term DAPT followed by ticagrelor monotherapy (i) is associated with a trend towards a reduced risk of MACE, (ii) significantly decreases all-cause mortality and the risk of NACE and major bleeding, and (iii) results in an unchanged risk of cardiovascular death, MI, ST, and stroke. See **Figure 4** for the summary of key outcomes.

The balance between ischemic and bleeding risks determines the overall benefit of antithrombotic treatments. Across all three included studies,[18–20] short-term DAPT followed by ticagrelor monotherapy resulted in an unchanged risk of MACE compared with standard DAPT. Although the TICO[18] and TWILIGHT trials[19] found significant increases of major bleeding events with standard DAPT, the GLOBAL LEADERS trial[20] could not detect a significant difference between the treatment groups. This is rather unexpected, as the GLOBAL LEADERS trial[20] compared the shortest DAPT duration (1 month) to standard DAPT—the other two trials[18,19] both compared 3-month DAPT to standard 12-month DAPT—which may have led to the assumption that it would show the greatest relative risk reduction of major bleeding. In contrast, the TWILIGHT trial[19] included both high-risk bleeding and ischemic patients and therefore expectedly demonstrated a significantly increased risk of major bleeding events in patients with standard DAPT. The TICO trial[18] excluded patients at increased risk of bleeding, yet still showed a significant decrease of major bleeding events in the short-term DAPT followed by ticagrelor monotherapy group.

Interestingly, short-term DAPT followed by ticagrelor monotherapy significantly decreased all-cause mortality compared with standard DAPT, which may be due to the accompanying decreased risk of major bleeding. Further studies investigating the particular concept of $P2Y_{12}$ inhibitor/ticagrelor monotherapy are needed to underscore and confirm this result. Indeed, the reduction of major bleeding following PCI is an important clinical aim, due to its strong association with mortality.[25] All three trials[18–20] in this analysis compared short-term DAPT followed by ticagrelor monotherapy to standard DAPT. Conceivably, it is easier to demonstrate less bleeding with a single antiplatelet therapy regimen than with a DAPT regimen, and our meta-analysis confirmed the significant reduction of major bleeding events with short-term DAPT followed by ticagrelor monotherapy compared with standard DAPT.

In contrast, short-term DAPT followed by ticagrelor monotherapy was associated with an unchanged relative risk of MACE compared with standard DAPT, even showing a trend toward fewer events in the ticagrelor monotherapy treatment group, which makes it an attractive and feasible treatment option in the future. This is further substantiated by the significant results in favor of short-term DAPT followed by ticagrelor monotherapy in our net clinical benefit analysis (**Figure 1b**).

Compared with ticagrelor monotherapy, aspirin monotherapy may have similar efficacy in reducing bleeding events, with potentially no increased risk of MACE. Each of the three clinical trials fall short of a duly needed third study arm, investigating the effects of short-term DAPT followed by aspirin monotherapy. The head-to-head comparison of short-term DAPT followed by aspirin vs. $P2Y_{12}$ inhibitor (ticagrelor in particular) monotherapy is, however, missing. Given the relatively inexpensive costs of aspirin compared with ticagrelor and increased risk of discontinuation due to side effects, such as dyspnea, a three-way study design would be of major interest. Two studies, the RESET[26] and the OPTIMIZE[27] trials, have investigated the concept of short-term DAPT (1–3 months) followed by aspirin monotherapy vs. standard DAPT (6–12 months). Both studies used zotarolimus-eluting stents only and found no change in ischemic and bleeding risk between groups.

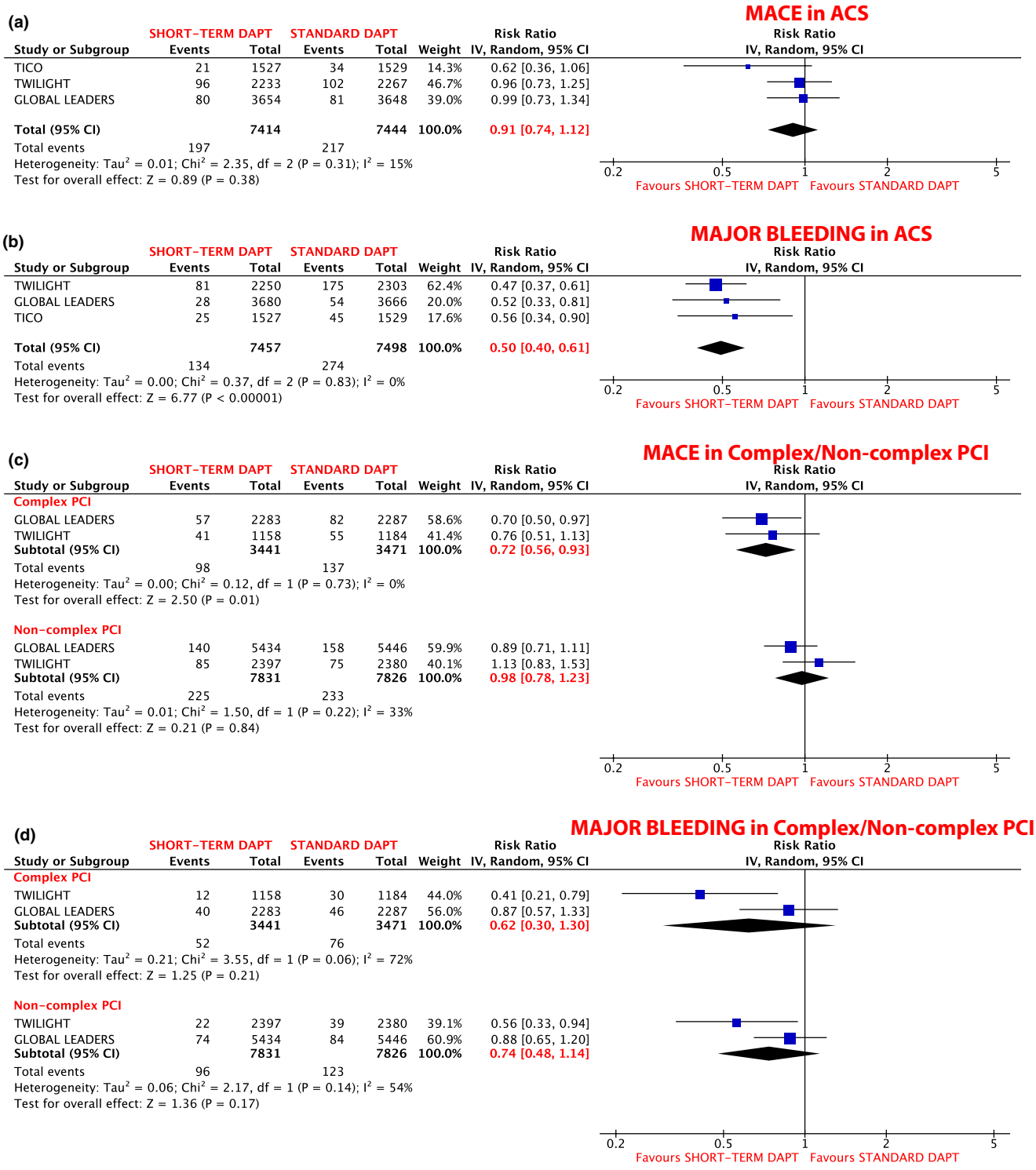

Figure 3 Subgroup analyses. Forest plot showing the risk ratio of (**a**) major adverse cardiovascular event (MACE) in patients presenting with acute coronary syndrome (ACS), (**b**) major bleeding in patients presenting with ACS, and (**c**) MACE in patients undergoing complex or noncomplex percutaneous coronary intervention (PCI), and (**d**) major bleeding in patients undergoing complex or noncomplex PCI according to the two treatment regimens: short-term dual antiplatelet therapy (DAPT) followed by ticagrelor monotherapy vs. standard DAPT.

Results from a meta-analysis comparing monotherapy with a $P2Y_{12}$ inhibitor vs. aspirin for secondary prevention of cardiovascular disease show that $P2Y_{12}$ inhibitor monotherapy was associated with a relative risk reduction of myocardial infarction but an unchanged risk of stroke, all-cause death, cardiovascular death, and major bleeding.[28] The benefit of $P2Y_{12}$ inhibitor monotherapy is, however, questionable due to the high number needed to treat to prevent myocardial infarction and the lack of effect on mortality.

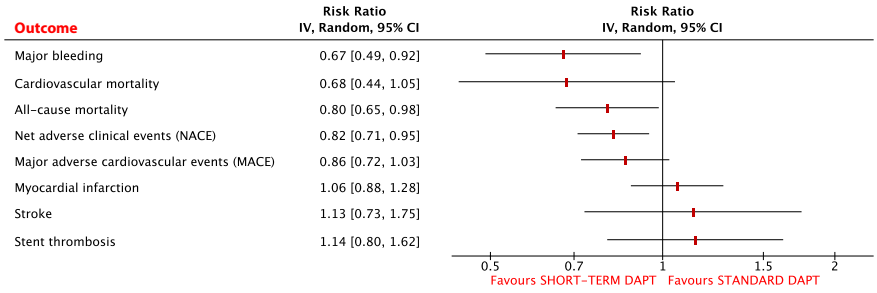

Figure 4 Forest plot showing the risk ratio of the key outcomes across the two treatment regimens: short-term dual antiplatelet therapy (DAPT) followed by ticagrelor monotherapy vs. standard DAPT.

Clinical implications

The available evidence shows that ticagrelor monotherapy might be effective and safe after an initial phase of DAPT. This might be of particular interest in patients with high bleeding risk. Importantly, a comparison of aspirin vs. ticagrelor monotherapy would be of great interest. Whether patients with high bleeding risk might benefit in terms of the net outcome from short-term DAPT with subsequent $P2Y_{12}$ inhibitor monotherapy compared with standard DAPT, is now additionally investigated in upcoming trials (A-CLOSE trial: NCT03947229 and SMART-CHOICEII trial: NCT03119012). For bleeding risk assessment, the PRECISE-DAPT score may be used.[29] The management of patients with both high ischemic and bleeding risk remains challenging and may necessitate an individualized antiplatelet approach.

Our meta-analysis further supports the use of short-term DAPT followed by ticagrelor monotherapy compared with standard DAPT in patients presenting with ACS, as it was associated with an unchanged ischemic risk and a significant reduction of bleeding events. Current ESC guidelines on the management of patients presenting without persistent ST-segment elevation MI have already incorporated the possibility of an aspirin-free treatment strategy, depending on the balance between the ischemic and bleeding risk (class IIa, level A recommendation).[30] This recommendation may be extended to patients presenting with ST-segment MI and patients with chronic coronary syndrome in the future.

The use of ticagrelor monotherapy following short-term DAPT may also be warranted in patients undergoing complex PCI, as it was associated with a lower ischemic and an unchanged bleeding risk compared with standard DAPT.

Limitations

Our meta-analysis has several limitations. First, its limited sample size, including only three trials and comprising a total of just 26,143 patients, precludes universal statements. Second, the patient population included was heterogenous and included patients at different ischemic and bleeding risks. One study only included patients presenting with ACS.[18] Third, this meta-analysis lacks patient-level data, which precludes the evaluation of relevant subgroups and renders the performance of an accurate time-to-event analysis impossible. Fourth, for the composite end point MACE in the GLOBAL LEADERS trial, all-cause mortality had to be used instead of cardiovascular mortality due to the unavailability of data. Fifth, this study assigns equal footing to the various outcomes of NACE despite differently weighted risks in real life.

CONCLUSION

Compared with standard DAPT, short-term DAPT followed by $P2Y_{12}$ inhibitor monotherapy with ticagrelor resulted in an unchanged ischemic risk but decreased all-cause mortality, the relative risk of NACE, and major bleeding. Direct comparisons of aspirin vs. $P2Y_{12}$ inhibitor monotherapy (in particular ticagrelor) after coronary stent implantation are needed.

Supporting Information

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICTS OF INTEREST

M.A.M. receives lecture fees from Daiichi Sankyo unrelated to the present manuscript. J.M.S.-M. receives lecture fees from Daiichi Sankyo, Chiesi, Astra Zeneca, Bayer, and BMS; all unrelated to the present manuscript. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

G.G. and J.M.S.M. wrote the manuscript. G.G. and J.M.S.M. designed and performed the research. G.G., C.S., B.J., G.M.G., A.M.D., M.A.M., B.P., P.V., and J.M.S.M. analyzed the data. All authors approved the final version of the manuscript.

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